WEST Search History

DATE: Sunday, July 27, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB; PLUR=NO; OP=ADJ			
L14	L13 same l10	3	L14
L13	sml1 or (sml adj 1)	35	L13
L12	L11 same l10	1	L12
L11	crt1 or (crt adj 1)	618	L11
L10	ribonucleotidereductase$1 or (ribonucleotide adj reductase$1) or RNR1 or RNR2 opr RNR3 or RNR4	1056	L10
DB=USPT; PLUR=NO; OP=ADJ			
L9	L7 and l2	0	L9
L8	L7 and l1	0	L8
L7	L3[ti,ab]	6	L7
L6	L1 same l3	0	L6
L5	L3 same l2	0	L5
L4	L3 with l2	0	L4
L3	crt1 or (crt adj 1)	498	L3
L2	RNR1 or RNR2 opr RNR3 or RNR4	15	L2
L1	ribonucleotidereductase$1 or (ribonucleotide adj reductase$1)	602	L1

END OF SEARCH HISTORY

L3 ANSWER 15 OF 17 MEDLINE on STN DUPLICATE 10

ACCESSION NUMBER: 92380659 MEDLINE
DOCUMENT NUMBER: 92380659 PubMed ID: 1511987
TITLE: Assignment of the gene for human spasmolytic protein (hSP/**SML1**) to chromosome 21.
AUTHOR: Theisinger B; Welter C; Grzeschik K H; Blin N
CORPORATE SOURCE: Institut fur Humangenetik, Universitat des Saarlandes, Homburg/Saar, Federal Republic of Germany.
SOURCE: HUMAN GENETICS, **(1992 Aug)** 89 (6) 681-2.
Journal code: 7613873. ISSN: 0340-6717.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199209
ENTRY DATE: Entered STN: 19921018
Last Updated on STN: 19921018
Entered Medline: 19920929

AB A human cDNA corresponding to the porcine pancreatic spasmolytic protein (PSP) was isolated, and the recombinant clone was originally termed hSP for human spasmolytic protein. Later, the term **SML1** for spasmolysin was suggested for the human gene. This protein shows a remarkable sequence homology to pS2, a protein coded by an estrogen-induced gene isolated from the breast carcinoma cell line MCF-7. Although, at the DNA level, the gene sequences pS2 and hSP/**SML1** display insufficient homology for cross-hybridization, their expression in tumor cells occurs with remarkable coordination. The human pS2 gene sequence has been assigned to chromosome 21, and we have therefore attempted to map the hSP/**SML1** gene by using cDNA and Southern blotting of genomic DNAs from a panel of human-rodent somatic cell hybrids carrying different complements of human chromosomes. Interestingly, the hSP/**SML1** gene is also localized on chromosome 21.

YBR1012 an essential gene from S. cerevisiae: construction of an RNA antisense conditional allele and isolation of a multicopy suppressor.

Nasr F, Becam AM, Slonimski PP, Herbert CJ.

C R Acad Sci III. 1994 Jul;317(7):607-13.

Centre de Génétique Moléculaire, Laboratoire propre du CNRS, l'Université Pierre-et-Marie-Curie, Gif-sur-Yvette, France.

The gene YBR1012 was identified during the systematic sequencing of chromosome II of the yeast Saccharomyces cerevisiae. We have inactivated the gene and shown that it is essential for cellular viability. Using antisense RNA technology we have constructed a conditional allele, expression of the antisense RNA strongly inhibits growth. To our knowledge this is the first successful use of antisense RNA technology in S. cerevisiae. Comparison of the deduced ybr1012p sequence with the data banks revealed the presence of a putative phosphatidylinositol kinase domain and a strong homology to the Schizosaccharomyces pombe rad3p. These results suggest that ybr1012p may be involved in signal transduction, possibly related to the control of replication and/or DNA damage repair. The link with DNA damage repair was reinforced by the isolation of the DUN1 gene as a multicopy suppressor of the YBR1012 deletion.

L6: Entry 38 of 39 File: USPT May 25, 1982

DOCUMENT-IDENTIFIER: US 4331662 A
TITLE: Methods for the treatment of viral infections

Application Filing Date (1):
19800204

Brief Summary Text (3):
Since ribonucleotide reductase is an essential substance in the metabolic cycle which leads to the synthesis of desoxyribonucleic acid, it is obvious that impairment of the activity of this enzyme results in an inhibition of the desoxyribonucleic acid synthesis in the cell. Hitherto, only one substance has become known, namely hydroxyurea, which inhibits the activity of ribonucleotide reductase not only in vitro but also in vivo (see I. H. Krakoff, N. C. Brown and P. Reichard, Cancer res., 28, 1559/1968; L. Skoog and B. Nordenskjold, Eur. J. Biochem., 19, 81/1971). Interesting results have been achieved with this compound not only with regard to the nucleotide metabolism but also with regard to the duplication of desoxyribonucleic acid (see L. Skoog and B. Nordenskjold, loc. cit.; G. Magnusson, R. Craig, M. Narkhammar, P. Reichard, M. Staub and H. Warner, Cold Spring Harbor Symp. on Quant. Biology, 29, 227/1975). However, hydroxyurea is a very reactive compound and its specificity for the in vivo inhibition of ribonucleotide reductase has already been doubted (see H.S. Rosenkranz, S. Jacobs and H. Carr, Biochimica et Biophysica Acta, 161, 428/1968).

L10 ANSWER 2 OF 8 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 2001:836523 SCISEARCH
THE GENUINE ARTICLE: 481VC
TITLE: Genomic expression responses to DNA-damaging agents and the regulatory role of the yeast ATR homolog Mec1p
AUTHOR: Gasch A P; Huang M X; Metzner S; Botstein D; Elledge S J; Brown P O (Reprint)
CORPORATE SOURCE: Stanford Univ, Sch Med, Dept Biochem, Stanford, CA 94305 USA (Reprint); Stanford Univ, Sch Med, Dept Genet, Stanford, CA 94305 USA; Stanford Univ, Sch Med, Howard Hughes Med Inst, Stanford, CA 94305 USA; Baylor Coll Med, Dept Biochem, Houston, TX 77030 USA; Baylor Coll Med, Howard Hughes Med Inst, Houston, TX 77030 USA
COUNTRY OF AUTHOR: USA
SOURCE: MOLECULAR BIOLOGY OF THE CELL, (OCT 2001) Vol. 12, No. 10, pp. 2987-3003.
Publisher: AMER SOC CELL BIOLOGY, 8120 WOODMONT AVE, STE 750, BETHESDA, MD 20814-2755 USA.
ISSN: 1059-1524.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 68
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Eukaryotic cells respond to DNA damage by arresting the cell cycle and modulating gene expression to ensure efficient DNA repair. The human ATR kinase and its homolog in yeast, **MEC1**, play central roles in transducing the damage signal. To characterize the role of the **Mec1** pathway in modulating the cellular response to DNA damage, we used DNA microarrays to observe genomic. expression in Saccharomyces cerevisiae responding to two different DNA-damaging agents. We compared the genome-wide expression patterns of wild-type cells and mutants defective in **Mec1** signaling, including **mec1**, dun1, and crt1 mutants, under normal growth conditions and in response to the methylating-agent methylmethane sulfonate (MMS) and ionizing radiation. Here, we present a comparative analysis of wild-type and mutant cells responding to these DNA-damaging agents, and identify specific features of the gene expression responses that are dependent on the **Mec1** pathway. Among the hundreds of genes whose expression was affected by Mec1p, one set of genes appears to represent an **MEC1**-dependent expression signature of DNA damage. Other aspects of the genomic responses were independent of Mec1p, and likely independent of DNA damage, suggesting the pleiotropic effects of MMS and ionizing radiation. The complete data set as well as supplemental materials is available at http://www-genome.stanford.edu/**mec1**.

L10 ANSWER 4 OF 8 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1999:727399 SCISEARCH
THE GENUINE ARTICLE: 237MM
TITLE: NORF5/HUG1 is a component of the **MEC1**-mediated checkpoint response to DNA damage and replication arrest in Saccharomyces cerevisiae
AUTHOR: Basrai M A (Reprint); Velculescu V E; Kinzler K W; Hieter P
CORPORATE SOURCE: NCI, DEPT GENET, DIV CLIN SCI, MED BRANCH, BETHESDA, MD 20889 (Reprint); JOHNS HOPKINS UNIV, SCH MED, DEPT MOL BIOL & GENET, BALTIMORE, MD 21205; JOHNS HOPKINS UNIV, SCH MED, CTR ONCOL, BALTIMORE, MD 21231; UNIV BRITISH COLUMBIA, CTR MOL MED & THERAPEUT, VANCOUVER, BC V5Z 4H4, CANADA
COUNTRY OF AUTHOR: USA; CANADA
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (OCT 1999) Vol. 19, No. 10, pp. 7041-7049.
Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171.
ISSN: 0270-7306.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 49

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Analysis of global gene expression in Saccharomyces cerevisiae by the serial analysis of gene expression technique has permitted the identification of at least 302 previously unidentified transcripts from nonannotated open reading frames (NORFs). Transcription of one of these, NORF5/HUG1 (hydroxyurea and UV and gamma radiation induced), is induced by DNA damage, and this induction requires **MEC1**, a homolog of the **ataxia telangiectasia** mutated (ATM) gene. DNA damage-specific induction of HUG1, which is independent of the cell cycle stage, is due to the alleviation of repression by the Crt1p-Ssn6p-Tup1p complex. Overexpression of HUG1 is lethal in combination with a **mec1** mutation in the presence of DNA damage or replication arrest, whereas a deletion of HUG1 rescues the lethality due to a **mec1** null allele. HUG1 is the first example of a NORF with important biological functional properties and defines a novel component of the **MEC1** checkpoint pathway.

L10 ANSWER 6 OF 8 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1998:755758 SCISEARCH
THE GENUINE ARTICLE: 123ZB
TITLE: Recovery from DNA replicational stress is the essential function of the S-phase checkpoint pathway
AUTHOR: Desany B A; Alcasabas A A; Bachant J B; Elledge S J (Reprint)
CORPORATE SOURCE: BAYLOR COLL MED, HOWARD HUGHES MED INST, VERNA & MARRS MCLEAN DEPT BIOCHEM, HOUSTON, TX 77030 (Reprint); BAYLOR COLL MED, HOWARD HUGHES MED INST, VERNA & MARRS MCLEAN DEPT BIOCHEM, HOUSTON, TX 77030
COUNTRY OF AUTHOR: USA
SOURCE: GENES & DEVELOPMENT, (15 SEP 1998) Vol. 12, No. 18, pp. 2956-2970.
Publisher: COLD SPRING HARBOR LAB PRESS, 1 BUNGTOWN RD, PLAINVIEW, NY 11724.
ISSN: 0890-9369.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 48

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB RAD53 and **MEC1** are essential genes required for the transcriptional and cell cycle responses to DNA damage and DNA replication blocks. We have examined the essential function of these genes and found that their lethality but not their checkpoint defects can be suppressed by increased expression of genes encoding **ribonucleotide reductase**. Analysis of viable null alleles revealed that **Mec1** plays a greater role in response to inhibition of DNA synthesis than Rad53. The loss of survival in **mec1** and rad53 null or point mutants in response to transient inhibition of DNA synthesis is not a result of inappropriate anaphase entry but primarily to an inability to complete chromosome replication. We propose that this checkpoint pathway plays an important role in the maintenance of DNA synthetic capabilities when DNR replication is stressed.

L10 ANSWER 8 OF 8 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 96:363287 SCISEARCH
THE GENUINE ARTICLE: UJ182
TITLE: DISTINCT ROLES OF YEAST MEC AND RAD CHECKPOINT GENES IN TRANSCRIPTIONAL INDUCTION AFTER DNA-DAMAGE AND IMPLICATIONS FOR FUNCTION
AUTHOR: KISER G L; WEINERT T A (Reprint)
CORPORATE SOURCE: UNIV ARIZONA, DEPT MOLEC & CELLULAR BIOL, TUCSON, AZ, 85721 (Reprint); UNIV ARIZONA, DEPT MOLEC & CELLULAR BIOL, TUCSON, AZ, 85721
COUNTRY OF AUTHOR: USA
SOURCE: MOLECULAR BIOLOGY OF THE CELL, (MAY 1996) Vol. 7, No. 5, pp. 703-718.
ISSN: 1059-1524.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 80

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In eukaryotic cells, checkpoint genes cause arrest of cell division when DNA is damaged or when DNA replication is blocked. In this study of budding yeast checkpoint genes, we identify and characterize another role for these checkpoint genes after DNA damage-transcriptional induction of genes. We found that three checkpoint genes (of six genes tested) have strong and distinct roles in transcriptional induction in four distinct pathways of regulation (each defined by induction of specific genes). **MEC1** mediates the response in three transcriptional pathways, RAD53 mediates two of these pathways, and RAD17 mediates but a single pathway. The three other checkpoint genes (including RAD9) have small (twofold) but significant roles in transcriptional induction in all pathways. One of the pathways that we identify here leads to induction of **MEC1** and RAD53 checkpoint genes themselves. This suggests a positive feedback circuit that may increase the cell's ability to respond to DNA damage. We make two primary conclusions from these studies. First, **MEC1** appears to be the key regulator because it is required for all responses (both transcriptional and cell cycle arrest), while other genes serve only a subset of these responses. Second, the two types of responses, transcriptional induction and cell cycle arrest, appear distinct because both require **MEC1** yet only cell cycle arrest requires RAD9. These and other results were used to formulate a working model of checkpoint gene function that accounts for roles of different checkpoint genes in different responses and after different types of damage. The conclusion that the yeast **MEC1** gene is a key regulator also has implications for the role of a putative human homologue, the ATM gene.

L13 ANSWER 1 OF 3 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 96422023 MEDLINE
DOCUMENT NUMBER: 96422023 PubMed ID: 8824640
TITLE: The Saccharomyces cerevisiae MEC1 gene, which encodes a homolog of the human ATM gene product, is required for G1 arrest following radiation treatment.
AUTHOR: Siede W; Allen J B; Elledge S J; Friedberg E C
CORPORATE SOURCE: Division of Cancer Biology, Department of Radiation Oncology and Winship Cancer Center, Emory University School of Medicine, Atlanta, Georgia 30322, USA.
CONTRACT NUMBER: CA12428 (NCI)
GM44644 (NIGMS)
SOURCE: JOURNAL OF BACTERIOLOGY, **(1996 Oct)** 178 (19) 5841-3.
Journal code: 2985120R. ISSN: 0021-9193.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 20020907
Entered Medline: 19961126

AB The Saccharomyces cerevisiae gene MEC1 represents a structural homolog of the human gene ATM mutated in ataxia telangiectasia patients. Like human **ataxia telangiectasia** cell lines, **mec1** mutants are defective in G2 and S-phase cell cycle checkpoints in response to radiation treatment. Here we show an additional defect in G1 arrest following treatment with UV light or gamma rays and map a defective arrest stage at or upstream of START in the yeast cell cycle.

L13 ANSWER 2 OF 3 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 96144686 MEDLINE
DOCUMENT NUMBER: 96144686 PubMed ID: 8553072
TITLE: Regulation of RAD53 by the ATM-like kinases MEC1 and TEL1 in yeast cell cycle checkpoint pathways.
COMMENT: Comment in: Science. 1996 Jan 19;271(5247):314-5
AUTHOR: Sanchez Y; Desany B A; Jones W J; Liu Q; Wang B; Elledge S J
CORPORATE SOURCE: Verna and Mars McLean Department of Biochemistry, Department of Molecular and Human Genetics, Howard Hughes Medical Institute, Baylor College of Medicine, Houston, TX 77030, USA.
CONTRACT NUMBER: DK07696 (NIDDK)
GM44664 (NIGMS)
SOURCE: SCIENCE, **(1996 Jan 19)** 271 (5247) 357-60.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 19960306
Last Updated on STN: 20020907
Entered Medline: 19960221

AB Mutants of the Saccharomyces cerevisiae **ataxia telangiectasia** mutated (ATM) homolog **MEC1**/SAD3/ESR1 were identified that could live only if the RAD53/SAD1 checkpoint kinase was overproduced. MEC1 and a structurally related gene, TEL1, have overlapping functions in response to DNA damage and replication blocks that in mutants can be provided by overproduction of RAD53. Both MEC1 and TEL1 were found to control phosphorylation of Rad53p in response to DNA damage. These results indicate that RAD53 is a signal transducer in the DNA damage and replication checkpoint pathways and functions downstream of two members of the ATM lipid kinase family. Because several members of this pathway are conserved among eukaryotes, it is likely that a RAD53-related kinase will function downstream of the human ATM gene product and play an important role in the mammalian response to DNA damage.

L13 ANSWER 3 OF 3 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 3
ACCESSION NUMBER: 1995:484543 BIOSIS
DOCUMENT NUMBER: PREV199598498843
TITLE: A checkpoint regulates the rate of progression through S phase in S. cerevisiae in response to DNA damage.
AUTHOR(S): Paulovich, Amanda G.; Hartwell, Leland H.
CORPORATE SOURCE: Univ. Washington, Dep. Genetics, Seattle, WA 98195 USA
SOURCE: Cell, (1995) Vol. 82, No. 5, pp. 841-847.
ISSN: 0092-8674.
DOCUMENT TYPE: Article
LANGUAGE: English
AB We demonstrate that in S. cerevisiae the rate of ongoing S phase is slowed when the DNA is subjected to alkylation. Slowing of replication is dependent on the MEC1 and RAD53 genes, indicating that lesions alone do not slow replication in vivo and that the slowing is an active process. While it has been shown that a MEC1- and RAD53-dependent checkpoint responds to blocked replication or DNA damage by inhibiting the onset of mitosis, we demonstrate that this checkpoint must also have an additional target within S phase that controls replication rate. MEC1 is a homolog of the human ATM gene, which is mutated in **ataxia telangiectasia** (AT) patients. Like **mec1** yeast, AT cells are characterized by damage-resistant DNA synthesis, highlighting the congruence of the yeast and mammalian systems.

L10 ANSWER 6 OF 8 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1998:755758 SCISEARCH
THE GENUINE ARTICLE: 123ZB
TITLE: Recovery from DNA replicational stress is the essential function of the S-phase checkpoint pathway
AUTHOR: Desany B A; Alcasabas A A; Bachant J B; Elledge S J (Reprint)
CORPORATE SOURCE: BAYLOR COLL MED, HOWARD HUGHES MED INST, VERNA & MARRS MCLEAN DEPT BIOCHEM, HOUSTON, TX 77030 (Reprint); BAYLOR COLL MED, HOWARD HUGHES MED INST, VERNA & MARRS MCLEAN DEPT BIOCHEM, HOUSTON, TX 77030
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LANGUAGE: English
REFERENCE COUNT: 48

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L13 ANSWER 2 OF 3 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 96144686 MEDLINE
DOCUMENT NUMBER: 96144686 PubMed ID: 8553072
TITLE: Regulation of RAD53 by the ATM-like kinases MEC1 and TEL1 in yeast cell cycle checkpoint pathways.
COMMENT: Comment in: Science. 1996 Jan 19;271(5247):314-5
AUTHOR: Sanchez Y; Desany B A; Jones W J; Liu Q; Wang B; Elledge S J
CORPORATE SOURCE: Verna and Mars McLean Department of Biochemistry, Department of Molecular and Human Genetics, Howard Hughes Medical Institute, Baylor College of Medicine, Houston, TX 77030, USA.
CONTRACT NUMBER: DK07696 (NIDDK)
GM44664 (NIGMS)
SOURCE: SCIENCE, **(1996 Jan 19)** 271 (5247) 357-60.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 19960306
Last Updated on STN: 20020907
Entered Medline: 19960221

AB Mutants of the Saccharomyces cerevisiae **ataxia telangiectasia** mutated (ATM) homolog **MEC1**/SAD3/ESR1 were identified that could live only if the RAD53/SAD1 checkpoint kinase was overproduced. MEC1 and a structurally related gene, TEL1, have overlapping functions in response to DNA damage and replication blocks that in mutants can be provided by overproduction of RAD53. Both MEC1 and TEL1 were found to control phosphorylation of Rad53p in response to DNA damage. These results indicate that RAD53 is a signal transducer in the DNA damage and replication checkpoint pathways and functions downstream of two members of the ATM lipid kinase family. Because several members of this pathway are conserved among eukaryotes, it is likely that a RAD53-related kinase will function downstream of the human ATM gene product and play an important role in the mammalian response to DNA damage.

L13 ANSWER 1 OF 3 MEDLINE on STN DUPLICATE 1

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DOCUMENT NUMBER: 96422023 PubMed ID: 8824640
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AUTHOR: Siede W; Allen J B; Elledge S J; Friedberg E C
CORPORATE SOURCE: Division of Cancer Biology, Department of Radiation Oncology and Winship Cancer Center, Emory University School of Medicine, Atlanta, Georgia 30322, USA.
CONTRACT NUMBER: CA12428 (NCI)
GM44644 (NIGMS)
SOURCE: JOURNAL OF BACTERIOLOGY, **(1996 Oct)** 178 (19) 5841-3.
Journal code: 2985120R. ISSN: 0021-9193.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 20020907
Entered Medline: 19961126

AB The Saccharomyces cerevisiae gene MEC1 represents a structural homolog of the human gene ATM mutated in ataxia telangiectasia patients. Like human **ataxia telangiectasia** cell lines, **mec1** mutants are defective in G2 and S-phase cell cycle checkpoints in response to radiation treatment. Here we show an additional defect in G1 arrest following treatment with UV light or gamma rays and map a defective arrest stage at or upstream of START in the yeast cell cycle.

L3 ANSWER 1 OF 17 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 1998448097 MEDLINE
DOCUMENT NUMBER: 98448097 PubMed ID: 9774971
TITLE: A suppressor of two essential checkpoint genes identifies a novel protein that negatively affects dNTP pools.
AUTHOR: Zhao X; Muller E G; Rothstein R
CORPORATE SOURCE: Department of Genetics and Development, Columbia University, College of Physicians and Surgeons, New York, New York 10032-2704, USA.
CONTRACT NUMBER: GM50237 (NIGMS)
SOURCE: MOLECULAR CELL, **(1998 Sep)** 2 (3) 329-40.
Journal code: 9802571. ISSN: 1097-2765.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 20030304
Entered Medline: 19981102

AB In Saccharomyces cerevisiae, MEC1 and RAD53 are essential for cell growth and checkpoint function. Their essential role in growth can be bypassed by deletion of a novel gene, **SML1**, which functions after several genes whose overexpression also suppresses mec1 inviability. In addition, **sml1** affects various cellular processes analogous to overproducing the large subunit of ribonucleotide reductase, RNR1. These include effects on mitochondrial biogenesis, on the DNA damage response, and on cell growth. Consistent with these observations, the levels of dNTP pools in **sml1** delta strains are increased compared to wild-type. This effect is not due to an increase in RNR transcription. Finally, both in vivo and in vitro experiments show that **Sml1** binds to Rnr1. We propose that **Sml1** inhibits dNTP synthesis posttranslationally by binding directly to Rnr1 and that Mec1 and Rad53 are required to relieve this inhibition.

Molecular Cell, Vol 2, 329-340, 1 September 1998

A Suppressor of Two Essential Checkpoint Genes Identifies a Novel Protein that Negatively Affects dNTP Pools

Xiaolan Zhao [1], Eric G. D. Muller [2], and Rodney Rothstein [1]‡*

[1]Department of Genetics and Development, Columbia University, College of Physicians and Surgeons, New York, New York 10032-2704, U

[2]Department of Biochemistry, University of Washington, Seattle, Washington 98195-7350, USA

Corresponding author: Rodney Rothstein, 212 305 1733 (phone), 212 923 2090 (fax)
rothstein@cuccfa.cc.columbia.edu

In *Saccharomyces cerevisiae*, *MEC1* and *RAD53* are essential for cell growth and checkpoint functio Their essential role in growth can be bypassed by deletion of a novel gene, *SML1*, which functions af several genes whose overexpression also suppresses *mec1* inviability. In addition, *sml1* affects variou cellular processes analogous to overproducing the large subunit of ribonucleotide reductase, *RNR1*. These include effects on mitochondrial biogenesis, on the DNA damage response, and on cell growth Consistent with these observations, the levels of dNTP pools in *sml1Δ* strains are increased compared wild-type. This effect is not due to an increase in *RNR* transcription. Finally, both in vivo and in vitro experiments show that Sml1 binds to Rnr1. We propose that Sml1 inhibits dNTP synthesis posttranslationally by binding directly to Rnr1 and that Mec1 and Rad53 are required to relieve this inhibition.

This article has been cited by the following articles:

- **The role of the Mre11-Rad50-Xrs2 complex in telomerase- mediated lengthening of *Saccharomyces cerevisiae* telomeres**
  Yasumasa Tsukamoto, Andrew K.P. Taggart and Virginia A. Zakian
  Current Biology, 2001, **11**:17:1328-1335
  [Summary] [Full Text] [PDF]
- **Targeted disruption of the cell-cycle checkpoint gene *ATR* leads to early embryonic lethality in mice**
  A. de Klein, M. Muijtjens, R. van Os, Y. Verhoeven, B. Smit, A.M. Carr, A.R. Lehmann and J.H.J. Hoeijmakers
  Current Biology, 2000, **10**:8:479-482
  [Summary] [Full Text] [PDF] [Supplemental Data]
- **Survival of DNA Damage in Yeast Directly Depends on Increased dNTP Levels Allowed by Relaxed Feedback Inhibition of Ribonucleotide Reductase**
  Andrei Chabes, Bilyana Georgieva, Vladimir Domkin, Xiaolan Zhao, Rodney Rothstein and Lars Thelander
  Cell, 2003, **112**:3:391-401
  [Summary] [Full Text] [PDF] [Supplemental Data]
- **Suppression of Spontaneous Chromosomal Rearrangements by S Phase Checkpoint Functions in *Saccharomyces cerevisiae***
  Kyungjae Myung, Abhijit Datta and Richard D. Kolodner
  Cell, 2001, **104**:3:397-408
  [Summary] [Full Text] [PDF]
- **Suppression of Spontaneous Chromosomal Rearrangements by S Phase Checkpoint Functions in *Saccharomyces cerevisiae***
  Kyungjae Myung, Abhijit Datta and Richard D. Kolodner
  Cell, 2001, **104**:3:397-408
  [Summary] [Full Text] [PDF]
- **The Isw2 Chromatin Remodeling Complex Represses Early Meiotic Genes upon Recruitment by Ume6p**
  Jesse P. Goldmark, Thomas G. Fazzio, Pete W. Estep, George M. Church and Toshio Tsukiyama
  Cell, 2000, **103**:3:423-433
  [Summary] [Full Text] [PDF]
- ***MEC1*-Dependent Redistribution of the Sir3 Silencing Protein from Telomeres to DNA Double-Strand Breaks**
  Kevin D. Mills, David A. Sinclair and Leonard Guarente
  Cell, 1999, **97**:5:609-620
  [Summary] [Full Text] [PDF]
- **Recovery from Checkpoint-Mediated Arrest after Repair of a Double-Strand Break Requires Srs2 Helicase**
  Moreshwar B. Vaze, Achille Pellicioli, Sang Eun Lee, Grzegorz Ira, Giordano Liberi, Ayelet Arbel-Eden, Marco Foiani and James E. Haber

Molecular Cell, 2002, **10**:2:373-385
[Summary] [Full Text] [PDF]

- **Rad9 Phosphorylation Sites Couple Rad53 to the *Saccharomyces cerevisiae* DNA Damage Checkpoint**
  Marc F. Schwartz, Jimmy K. Duong, Zhaoxia Sun, Jon S. Morrow, Deepti Pradhan and David F. Stern
  Molecular Cell, 2002, **9**:5:1055-1065
  [Summary] [Full Text] [PDF]
- **Only Connect: Linking Meiotic DNA Replication to Chromosome Dynamics**
  Susan L. Forsburg
  Molecular Cell, 2002, **9**:4:703-711
  [Summary] [Full Text] [PDF]
- **Lcd1p Recruits Mec1p to DNA Lesions In Vitro and In Vivo**
  John Rouse and Stephen P. Jackson
  Molecular Cell, 2002, **9**:4:857-869
  [Summary] [Full Text] [PDF] [Supplemental Data]
- **A DNA Damage Response Pathway Controlled by Tel1 and the Mre11 Complex**
  Takehiko Usui, Hideyuki Ogawa and John H.J. Petrini
  Molecular Cell, 2001, **7**:6:1255-1266
  [Summary] [Full Text] [PDF]
- **Dynamic Interaction of DNA Damage Checkpoint Protein Rad53 with Chromatin Assembly Factor Asf1**
  Andrew Emili, David M. Schieltz, John R. Yates and Leland H. Hartwell
  Molecular Cell, 2001, **7**:1:13-20
  [Summary] [Full Text] [PDF]
- **DNA Binding Hairpin Polyamides with Antifungal Activity**
  Nicholas J. Marini, Ramesh Baliga, Matthew J. Taylor, Sarah White, Paul Simpson, Luong Tsai and Eldon E. Baird
  Chemistry and Biology, 2003, **10**:7:635-644
  [Summary] [Full Text] [PDF]
- **Regulated Displacement of TBP from the *PHO8* Promoter In Vivo Requires Cbf1 and the Isw1 Chromatin Remodeling Complex**
  Jean-Luc Moreau, Melanie Lee, Nyasha Mahachi, Jay Vary, Jane Mellor, Toshio Tsukiyama and Colin R. Goding
  Molecular Cell, 2003, **11**:6:1609-1620
  [Summary] [Full Text] [PDF]

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L2: Entry 1 of 2 File: USPT Jun 16, 1998

DOCUMENT-IDENTIFIER: US 5767134 A
**** See image for Certificate of Correction ****
TITLE: Prodrug forms of ribonucleotide reductase inhibitors 3-AP and 3-AMP

US Patent No. (1):
5767134

Brief Summary Text (7):
Structure-activity relationship studies of a series of HCTs revealed that both 3-AP and 3-AMP showed much better therapeutic effects against L1210 leukemia, M- 109 lung carcinoma and A2780 human ovarian carcinoma than other HCTs reported to date. Liu, et al., J. Med. Chem. 1992, 35, 3672-3677; Agrawal, et al., "The Chemistry and Biological Activity of the .alpha.-(N)-Heterocyclic Carboxaldehyde Thiosemicarbazones." Progress in Medicinal Chemistry; Ellis, G. P.; West, G. B., Eds.; Elsevier/North-Holland Biomedical Press: New York, 1978; Vol. 15, pp 321-356. In addition, 3-AP and 3-AMP are potent agents with significant antineoplastic activity in comparison with hydroxyurea (HU), an approved ribonucleotide reductase inhibitor used in clinics.

Brief Summary Text (13):
It is yet another object of the invention to provide a method of treating neoplasia in animal or human patients utilizing the prodrug compounds of the instant invention.

Brief Summary Text (16):
The prodrugs of the present invention are useful in the treatment of neoplasia in animal or human patients. In vivo, these prodrugs are metabolized to produce the active therapeutic agents 3-AP or 3-AMP. Comparisons between administration of the instant prodrugs and the parent therapeutic agents to combat the growth of solid tumors in mammals demonstrate the increased efficacy of the prodrugs. Particularly preferred embodiments of the prodrugs of the invention include prodrugs I and II, below, which are organophosphate derivatives of 3-AP, the organophosphate group being linked to 3-AP through a urethane moiety at the 3-amino position; and prodrug III, which is a disulfide derivative of 3-AP, the disulfide group being linked to 3-AP through a urethane moiety at the 3-amino position. Also preferred are the analogous prodrug forms of 3-AMP. ##STR3##

Detailed Description Text (2):
The term "patient" is used throughout the specification to describe an animal, including a mammal such as a human, to whom treatment with the compositions according to the present invention is provided. For treatment of those infections, conditions, or disease states which are specific for a specific animal such as a human patient, the term patient refers to that specific animal.

Detailed Description Text (5):
The term "therapeutically effective amount" is used throughout the specification to describe that amount of the compound according to the present invention which is administered to a mammalian patient, especially including a human patient, suffering from cancer, to reduce or inhibit the growth or spread of the hematogenous, ascitic or solid tumor. Preferably, the compounds according to the present invention will result in a remission of the malignant hematogenous, ascitic or solid tumor. In the case of solid tumors, the compounds according to the present invention will inhibit

the further growth of the tumor tissue and preferably shrink the existing tumor.

Detailed Description Text (25):
The therapeutic aspect according to the present invention relates to methods for treating neoplasia in animal or human patients, in particular tumors in humans comprising administering antineoplastic effective amounts of the prodrug compounds according to the present invention to inhibit further growth of the neoplasms, bring that growth under control and preferably, produce a remission of the tumor. In the method of the present invention, a therapeutically effective amount of at least one prodrug according to the present invention is administered to a patient suffering from cancer, or a malignant or non-malignant tumor to inhibit the growth or spread of such cancer or tumor. Preferably, in the therapeutic aspect of the present invention, a therapeutically effective amount will result in a remission of the cancer or hematogenous ascitic or solid tumor. Preferably, in the case of solid tumors, the tumor will actually shrink in size.

Detailed Description Text (26):
Pharmaceutical compositions based upon these prodrug compounds comprise the above described compounds in a therapeutically effective amount for treating neoplasia, optionally in combination with a pharmaceutically acceptable additive, carrier or excipient. One of ordinary skill in the art will recognize that a therapeutically effective amount will vary with the condition to be treated, its severity, the treatment regimen to be employed, the pharmacokinetics of the agent used, as well as the patient (animal or human) treated.

Detailed Description Text (34):
The compounds and compositions according to the present invention are used to treat cancer in mammals, including humans. Generally, to treat malignant tumors, the compositions will be administered in parenteral, preferably intravenous dosage form in amounts ranging from about 10 micrograms up to about 500 mg or more one to four times per day. The present compounds are preferably administered orally, but they also may be administered in an alternative manner, for example, parenterally or even topically or in suppository form.

CLAIMS:

10. A method for treating neoplasia in animal or human patients, comprising; administering a therapeutically effective amount of a compound according to the formula: ##STR11## where R.sup.4 is H or CH.sub.3, R.sup.5 is CH.sub.2 or ##STR12## and R.sup.8 is CH.sub.2 CH.sub.2 NH.sub.2, CH.sub.2 CH.sub.2 NHAc, CH.sub.2 CH.sub.2 OH or CH.sub.2 CO.sub.2 H.

13. A method for treating neoplasia in animal or human patients comprising administering a therapeutically effective amount of a compound according to the formula: ##STR13## where R.sup.4 is H or CH.sub.3 and

R.sup.5 is CHR, benzyl or ortho or para substituted benzyl;

R is H, CH.sub.3, CH.sub.2 CH.sub.3, CH.sub.2 CH.sub.2 CH.sub.3 or ##STR14## R' is a free acid phosphate, phosphate salt or an --S--S--R" group; R" is CH.sub.2 CH.sub.2 NHR.sup.6, CH.sub.2 CH.sub.2 OH, CH.sub.2 COOR.sup.7, an ortho or para substituted C.sub.1 -C.sub.3 alkylphenyl and ortho or para substituted nitro-phenyl;

R.sup.6 is H, C.sub.1 -C.sub.4 acyl group, trifluoroacetyl, benzoyl or substituted benzoyl group, and

R.sup.7 is H, C.sub.1 -C.sub.4 alkyl or a benzyl or substituted benzyl.

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L2: Entry 8 of 8 File: USPT Nov 10, 1998

DOCUMENT-IDENTIFIER: US 5834279 A
TITLE: Methods of identifying compounds that inhibit DNA synthesis in mycobacterium tuberculosis and compositions, reagents and kits for performing the same

Other Reference Publication (13):
Liuzzi, M. et al., "A Potent Peptidomimetic Inhibitor of HSV Ribonucleotide Reductase With Antiviral Activity in vivo", Nature, 1994, 372, 695-698.

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L6: Entry 29 of 39 File: USPT Mar 8, 1994

DOCUMENT-IDENTIFIER: US 5292775 A
**** See image for Certificate of Correction ****
TITLE: Anti-neoplastic, anti-viral and ribonucleotide reductase activity affecting pharmaceutical compositions and methods of treatment

Application Filing Date (1):
19921221

Brief Summary Text (11):
The present invention provides pharmaceutical compositions in unit dosage form adapted for administration to a human or non-human animal comprising a) an anti-neoplastic, anti-viral, anti-psoriasis, anti-malarial or ribonucleotide reductase activity affecting, effective amount of a compound of the formula:
##STR1## R is H or OH x is 3 or 4,

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L6: Entry 10 of 39 File: USPT Jun 16, 1998

DOCUMENT-IDENTIFIER: US 5767134 A
**** See image for Certificate of Correction ****
TITLE: Prodrug forms of ribonucleotide reductase inhibitors 3-AP and 3-AMP

Application Filing Date (1):
19970515

Brief Summary Text (4):
Cancer is one of the leading causes of death known today, and effective treatment of many solid tumors remains elusive. It is believed that novel antitumor drugs possessing a strong inhibitory effect on ribonucleotide reductase, an essential enzyme for cellular replication, would be a useful addition to present drug regimens for treating cancer.

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L6: Entry 2 of 39 File: USPT Mar 13, 2001

DOCUMENT-IDENTIFIER: US 6200754 B1
TITLE: Inhibitors of alternative alleles of genes encoding products that mediate cell response to environmental changes

Application Filing Date (1):
19980319

Brief Summary Text (39):
In preferred embodiments of above aspects, a conventional therapy acts on a protein or other molecular target in the same pathway as the allele specific inhibitor. As an example, the antineoplastic drug hydroxyurea, which inhibits ribonucleotide reductase (RR), can be used in conjunction with an allele specific inhibitor of RR subunit M1 or M2 or or another gene that encodes a product important in nucleotide synthesis. Similarly, the antiproliferative drug methotrexate inhibitos the enzyme dihydrofolate reductase (DHFR), and can be used with allele specific inhibitors of DHFR that would result in a differential methotrexate effect on cancer tissues compared to normal proliferating tissues. Alternatively, methotrexate can be used with allele specific inhibitors of other genes important in folate metabolism to achieve an enhanced cancer cell specificity for methotrexate. Similarly, the anticancer drug 5-flurouracil and related compounds can be administered together with an allele specific inhibitor of thymidylate synthase (TS) in a patient heterozygous for TS and with LOH at the TS gene in proliferating cells, e.g., cancer cells. Alternatively, an allele specific inhibitor of 5-FU degradation or metabolism can be administered with 5-FU. For example, the enzyme dihydropyrimidine dehydrogenase, which catalyzes the first and rate limiting step in 5-FU catabolism would have the effect of potentiating 5-FU action in cancer cells due to their lesser ability to metabolically inactivate 5-FU. One skilled in the art will readily recognize that similar methods can be used with other conditionally essential genes, incuding specific genes listed in the table of conditionally essential genes.

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L3: Entry 3 of 7 File: USPT Nov 10, 1998

DOCUMENT-IDENTIFIER: US 5834279 A
TITLE: Methods of identifying compounds that inhibit DNA synthesis in mycobacterium tuberculosis and compositions, reagents and kits for performing the same

Brief Summary Text (66):
Antibodies that specifically bind to an M. tuberculosis R2 protein or topoisomerase I protein are provided. Such antibodies are specific inhibitors of M. tuberculosis ribonucleotide reductase and topoisomerase I protein, respectively. Such antibodies may be used in methods of isolating a pure M. tuberculosis R2 protein and topoisomerase I protein, respectively. Likewise, such antibodies may be used in methods of inhibiting M. tuberculosis ribonucleotide reductase enzyme activity and topoisomerase I protein activity, respectively.

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L3: Entry 2 of 7 File: USPT Mar 23, 1999

DOCUMENT-IDENTIFIER: US 5885830 A
TITLE: Anti-ribonucleotide reductase R2 subunit monoclonal antibody

Abstract Text (1):
An anti-ribonucleotide reductase (RNR) R2 subunit monoclonal antibody KM1054, KM1056 or KM1060, which belongs to the IgG2a subclass, reacts with R2 subunit of RNR, and inhibits RNR activity, is disclosed. It is effective for immunologically detecting RNR and for immunologically detecting the presence of human cancer cells.

Brief Summary Text (2):
The present invention relates to a monoclonal antibody which is specifically reactive with a ribonucleotide reductase R2 subunit and which inhibits ribonucleotide reductase activity, as well as a hybridoma cell line producing the monoclonal antibody. The present invention further relates to a method of immunologically detecting a ribonucleotide reductase R2 subunit using the monoclonal antibody.

Other Reference Publication (11):
Engstrom, "Monoclonal Antibodies Against Mammalian Ribonucleotide Reductase", Acta Chemica Scandinavia, vol. B36, No. 5, pp. 343 and 344.

CLAIMS:

4. A method for in vitro detection of human ribonucleotide reductase R2 subunit using the monoclonal antibody as claimed in claim 1.

L6: Entry 35 of 39 File: USPT Nov 18, 1986

DOCUMENT-IDENTIFIER: US 4623659 A
TITLE: Polyhydroxybenzoic acid derivatives

Application Filing Date (1):
19830523

Detailed Description Text (66):
Compounds represented by formula I above have the ability to inhibit ribonucleotide reductase, an enzyme involved in the reductive conversion of ribonucleotides to deoxyribonucleotides. This enzymatic reaction is a rate controlling step in the biosynthetic pathway leading to DNA and cell replication. In general, the ribonucleotide reductase level is closely correlated with cellular replication. Thus, it is not surprising that the compounds of this invention, which are potent ribonucleotide reductase inhibitors, are also capable of prolonging the life of mice carrying transplanted tumors since replication of tumor cells is equally inhibited. In particular, we have found that administration of a compound of this invention coming within the scope of formula I above prolongs the life of mice inoculated with L1210 leukemia, a tumor not ordinarily susceptible to chemotherapy. In addition, the compounds have shown activity against P388 leukemia and B16 melanoma.

CLAIMS:

14. A method of inhibiting ribonucleotide reductase which comprises administering to a mammal carrying a tumor having a relatively high ribonucleotide reductase level, an amount of a compound according to the following formula effective to inhibit ribonucleotide reductase ##STR21## wherein n is 2-5; m is 0 or 1, R" is H or OH, R' is NOH or NH; R is NH.sub.2 or NHOH when R' is NOH; R is NH.sub.2 or O--C.sub.1-3 alkyl when R' is NH; with the proviso that, when m is 0 and R' is NOH, R cannot be NH.sub.2 ; or a pharmaceutically acceptable acid addition salt thereof.

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L6: Entry 30 of 39 File: USPT Aug 3, 1993

DOCUMENT-IDENTIFIER: US 5232939 A
**** See image for Certificate of Correction ****
TITLE: Use of imidazopyrazole derivatives as analgesics and anti-inflammatory agents

Application Filing Date (1):
19911118

Other Reference Publication (5):
Chemical Abstracts, vol. 95, No. 5, 1981, p. 32, column 2, abstract No. 35305s, Columbus, Ohio, US; A. Sato et al.: "Evaluation of combinations of drugs that inhibit Ehrlich tumor cell ribonucleotide reductase", & Cancer Res. 1981, 41(5), 1637-41 *Pyrazolomididazole*.